AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figures 1A-1F. These sheets, which include Figures 1A-1F, replace the original sheets including Figures 1A-1F.

REMARKS

Upon entry of this amendment, Claims 1-37, 39, 40, 42-63, and 65 constitute the pending claims in the present application. Among them, Claims 1-27, 47, 56-62, and 65 are directed to non-elected inventions and are withdrawn from further consideration. Applicants will cancel these claims upon indication of allowable subject matter as appropriate.

To expedite prosecution, Applicants have also cancelled Claim 38 without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future divisional or continuation applications. Dependent Claims 39, 40, and 42 are amended to depend on Claim 37. Claim 41 is also cancelled without prejudice due to these amendments.

Applicants thank the Examiner for withdrawing the species election requirement for elected Group IV and rejoining Claims 32 and 43-45.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Drawings

The Office Action objects Figures 1A-1F, because reference numbers 1-41 therein are not separately described in the Brief Description of the Figures section of the specification.

Applicants submit herewith replacement drawings for Figures 1A-1F, deleting the reference numbers 1-41, thereby obviating this objection. No new matter is introduced due to this drawing amendment. Reconsideration and withdrawal of objection are respectfully requested.

Claim Objections

Claim 42 is objected to because of the allegedly redundant recitation of "FK506" and "FK506 derivative." The Examiner suggests Applicants to delete "FK506 derivative" to obviate this objection.

Applicants have adopted the Examiner's suggestion to amend Claims 42 and 48, thereby

obviating this objection. Reconsideration and withdrawal of objection are respectfully requested.

Claim Rejection under 35 U.S.C. § 112, second paragraph

Claim 45 is rejected for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Office Action asserts that the phrase "involves the use of a cell providing an N-end rule degradation system" is allegedly unclear, because the claim allegedly does not provide the relationship between the cell with the N-end rule degradation system and the method steps of the three-hybrid assay of claims 43 or 44. It appears to be unclear to the Examiner how the cell is used in the assay. The Examiner has suggested claim language that would overcome this rejection.

To expedite prosecution, Applicants have adopted the Examiner's suggestion to amend Claim 45, thereby obviating this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejection under 35 U.S.C. § 102

Claims 28, 30, 31, 33, 34, 52, and 53 are rejected for allegedly being anticipated in view of Keenan *et al.* (*Bioorg. Med. Chem.* **6**: 1309-1335, 1998, or "Keenan") as evidenced by Amara *et al.* (*P.N.A.S. U.S.A.* **94**: 10618-10623, 1997, or "Amara") and Bierer *et al.* (*P.N.A.S. U.S.A.* **87**: 9231-9235, 1990, or "Bierer").

Applicants respectfully disagree for two reasons.

First of all, Applicants have previously argued (in the response filed on May 19, 2006), and hereby reiterate that Keenan fails to teach a screening method to identify a polypeptide that binds to a user-specified ligand, as is claimed in Claim 28. In Keenan, a number of ligands with *varying* linkers and/or *varying* binding monomers were tested for their relative abilities to *dimerize* known binding partners for the monomers. The question being asked in Keenan is: what linker-monomer combination offers the best dimerization of a known binding partner.

Thus, if there is any screening involved, it is a screen for the linker and/or monomer, not any binding partner (*e.g.*, the candidate ligand binding domain of Claim 28) that binds the monomer.

Thus, Keenan never teaches or suggests any screening assay in which a library of candidate binding proteins are to be expressed in cells, so that those candidate binding proteins that actually bind one of the two monomers on the ligand (R2) can be identified.

In other words, Keenan never teaches or suggests a candidate ligand-binding domain P2 as in Claim 28 (step (ii)(c)), since both ligand-binding domains in Keenan are *already known* and *invariable*. In fact, the Examiner agrees (on page 17, first paragraph of the January 6, 2006 Office Action) that Keenan fails to teach the screening of a library of nucleic acid sequences (encoding candidate P2).

Secondly, because of the nature and purpose of the Keenan assay, Applicants submit that Keenan does not perform a step according to step (v) of Claim 28, since, as mentioned before, Keenan does not perform any screening. There is no need in Keenan to "identify the nucleic acid sequence" of the second chimeric gene, because all the binding partners are known or predetermined.

In her response to Applicants' argument, the Examiner argues that "the features upon which applicant relies (i.e., library of candidate binding proteins and a ligand where R1 is different from R2) are not recited in the rejected claim(s)... Keenan et al test hybrid ligands that meet the structural limitations of the claims in the three-hybrid assay to identify whether the DNA binding domain and activation domain fusion proteins are capable of binding."

Applicants submit that: (1) the above arguments does not rely on "R1 being different from R2," (2) the untaught candidate ligand-binding domain P2 is in fact an element (*see* steps (ii) and (iii)) recited in the method steps of Claim 28, and (3) the untaught step (v) is a required step in Claim 28.

Therefore, Keenan fails to teach at least the candidate ligand-binding domain P2 and step (v), and thus cannot anticipate Claim 28 and its dependent claims 30, 31, 33, 34, 52, and 53. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejection under 35 U.S.C. § 103

Claims 54 and 55 are rejected for allegedly being obvious over Keenan et al. (*supra*) as evidenced by Amara et al. (*supra*) in view of Mehta. (*supra*).

Since Claims 54 and 55 both depend on Claim 28, if Claim 28 are non-obvious over Keenan as evidenced by Amara in view of Mehta, dependent Claims 54 and 55 are also non-obvious.

Even assuming, for the sake of argument, that there is motivation to combine the cited references, Applicants submit that the combined teachings still fail to teach or suggest the screening methods of Claim 28.

As argued above, Keenan is not interested in *identifying* any proteins that bind to R2, as evidence by the lack of teaching regarding at least the candidate ligand-binding domain P2 and step (v) of Claim 28. The same applies to Amara, which is concerned with dimerizing known proteins, not with screening for an unknown protein. Thus, even assuming Keenan and Amara can properly be combined with each other, the combination of the two references would still fail to teach or suggest a screening method with the requisite candidate ligand-binding domain P2 and step (v) of Claim 28. Mehta would not remedy this deficiency even if there were additional motivation to combine Mehta.

Furthermore, Claim 28 also requires a particular structure for the linker, which structure is unobvious over Keenan for the reasons below, and neither Amara nor Mehta remedies this deficiency either.

Specifically, Keenan teaches away from PEG linkers (*e.g.*, **1q** – **1r**) as recited in Claim 28, because Keenan indicates that the ability of these PEG linkers to "induce apoptosis in the Fas assay was poor" (p. 1313, 2nd column, 2nd full para. of Keenan). In Keenan, a variety of linkers were screened to see if any of them would outperform the hybrid ligand **1d**, which is the reference compound with an apoptosis IC_{50} of 6 nM, and transcription assay EC_{50} of 15 nM (transient transfection assay) or 20 nM (stable transfection assay). *See* table 1 on page 1311 of Keenan. Compounds **1i** - **1s** each shares the same FKBP12-binding monomer as that of **1d**, but differs in their respective linker sequences (*see* Table 1, pages 1311-1312; right column, page

1313, to left column, page 1314). Based on these assays, Keenan concludes that the three polyether linkers tested in ligands **1p – 1r**, described as "[a] more radically altered set of compounds" (page 1313, right column, towards the middle of the last para.), are "poor" in terms of their ability to induce apoptosis.

For example, the reference linker in **1d** has an IC_{50} of about 6 nM. In contrast, the best of **1p – 1r** has an IC_{50} of about 140 nM, about 25 times worse than **1d**. The same linkers (**1p – 1r**) are also considerably worse than **1d** in both the stable and the transient transfection assay, with EC_{50} between 5-20 times worse than that of **1d** (see Table 1 on page 1312). Overall, among the 11 linkers similarly tested, all but one (**1o**) are better than the polyether linkers in both the apoptosis assay and the transient transfection assay (see Table 1).

Note that linker AP1427 (**1k**) is not a polyethylene linker as recited in the pending claims, because it contains other non-polyethylene moieties (*e.g.*, it does not fit the general formula $(CH_2\text{-}X\text{-}CH_2)_n$ as required by the claims).

Since a skilled artisan would have had no motivation to use any of the worst linkers tested, Keenan teaches away from the PEG linkers recited in Claim 28, and thus Claim 28 and its dependent claims are additionally non-obvious over Keenan (or its combination with Amara and/or Mehta) for the reason above.

Therefore, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 43-45 are rejected for allegedly being obvious in view of Johnsson *et al.* (U.S. Pat. No. 5,585,245, cited as reference P04 on the IDS filed 4/26/2003; entire reference) in view of Licitra *et al.* (*P.N.A.S. U.S.A.* **93**: 12817-12821, 1996, "Licitra") as evidenced by Varshavsky *et al.* (*P.N.A.S. U.S.A.* **93**: 12142-12149, 1996, "Varshavsky").

Applicants have amended Claims 43 and 44 to further clarify the subject matter claimed. Amended Claims 43 and 44 recite specific linker Y structure (*e.g.*, PEG linker), which is not taught or suggested by Johnsson or Licitra.

The amended claims reciting the PEG linker structure are also non-obvious over any possible combinations of the art cited against other claims, because Licitra *teaches away* from improving the linker in its hybrid ligand, by suggesting that a better approach would be to

"generate yeast strains that are more permeable without significantly affecting yeast viability" (*see* page 12820, middle of the right column).

In addition, both Keenan (*supra*) and Bertozzi (*infra*) teach away from using the PEG linkers.

Therefore, Claims 43-45 as amended are non-obvious over the cited art. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 28-34, 36, 46, 48-50, and 53 are rejected for allegedly being obvious over Liu *et al.* (US Patent No. 5,928,868, entire reference, "Liu") in view of Bertozzi *et al.* (*J. Org. Chem.* **56**: 4326-4329, 1991, reference CC on IDS filed 7/20/2005, entire reference, "Bertozzi").

Claims 28-36, 46, 48-50, 52, and 53 are rejected for allegedly being obvious over Liu in view of Bertozzi and Lin *et al.* (*Journal of the American Chemical Society* **122**: 4247-4248 and S1-S12, published online 4/13/2000, cited in a prior action, entire reference, "Lin").

Claims 28-34, 36, 46, and 48-53 are rejected for allegedly being obvious over Liu in view of Bertozzi and Karlsson *et al.* (US Patent No. 6,143,574, cited in a prior action, entire reference, "Karlsson").

Claims 28-34, 36, 46, 48-50, 52, 53, and 63 are rejected for allegedly being obvious over Liu in view of Bertozzi and Licitra.

Claims 28-34, 36-42, 46, 48-50, 52, and 53 are rejected for allegedly being obvious over Liu in view of Bertozzi and Zaharevitz *et al.* (*Cancer Research* **59**: 2566-2569, 1999, entire reference, "Zaharevitz").

Applicants note that all these rejections rely on combining the respective teachings (especially Liu) with Bertozzi. The Office Action indicates that Liu does not teach the PEG linker, while Bertozzi allegedly makes up this deficiency.

Applicants respectfully disagree. Applicants submit that there is no motivation to combine Liu with Bertozzi, since Bertozzi *teaches away* from using the PEG linker in the screening methods described in Liu.

Specifically, Bertozzi discloses the use of PEG as linker moiety in heterodimeric hybrid ligands with increased water solubility (hydrophilicity), as well as the chemistry and synthesis of such ligands. Bertozzi emphasizes on page 4326 (right column, line 2) that PEG linkers are water-soluble, often highly so.

In contrast, Liu describes a cell-based *in vivo* screening method using hybrid ligands. An improved membrane permeability of the heterodimeric hybrid ligands is of utmost importance for such *in vivo* application to succeed. *See* Applicants' discussion about Licitra (*supra*); coauthor Liu is the inventor of US Patent No. 5,928,868.

As a skilled artisan will appreciate, biological membranes are highly *hydrophobic* (*i.e.*, not hydrophilic). Thus, when attempting to provide improved membrane-permeable heterodimeric hybrid ligands useful for *in vivo* application, such as the screening assay in Liu, a skilled artisan would be motivated to look for *hydrophobic* moieties, rather than hydrophilic moieties, such as those PEG linkers disclosed in Bertozzi. In other words, a skilled artisan would have had no motivation to use ligands incorporating such a linker for *in vivo* use, because the PEG linkers are known to be hydrophilic, and therefore would be expected to decrease membrane permeability of the ligand. Even if the PEG linker provided some benefit to link moieties A and B of the hybrid ligand in Liu, such benefit is certainly outweighed by the paramount importance of *membrane permeability* required of such hybrid ligand.

None of the other cited art makes up this deficiency, or provides any teaching or suggestion to the contrary that would have prompted a skilled artisan to combine Liu with Bertozzi.

It is the surprising finding by Applicants that the use of PEG linkers in accordance with the present invention actually increases the cellular uptake of the hybrid ligands, as shown in Figures 6 and 7 and Example 7, that leads to the claimed invention. This surprising effect was not predictable, and thus would have been non-obvious to a person skilled in the art in view of the Bertozzi teaching and the known water solubility of polyethylene glycols.

Therefore, reconsideration and withdrawal of the rejections are respectfully requested.

Claims 38-40 and 42 are rejected for allegedly being obvious over Liu in view of Zaharevitz.

As indicated above, to expedite prosecution, Applicants have cancelled Claim 38 without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future divisional or continuation applications. Dependent Claims 39, 40, and 42 are amended to depend on Claim 37. Claim 41 is also cancelled without prejudice due to these amendments.

This rejection is thus rendered moot.

Claims 28-34, 36, 46, 48-50, 52, and 53 are rejected for allegedly being obvious over Liu in view of Holt *et al.* (WO 96/06097, cited as reference AD on IDS filed 4/28/2003, entire reference, or "Holt"). The Office Action asserts that Liu fails to teach the PEG linker, while Hold makes up this deficiency. Applicants respectfully disagree.

Holt describes compounds that may be used to dimerize immunophilins (*e.g.*, FKBP, which binds FK506). The compounds of Holt contain a linker L, but Holt only generically suggests that the linker L "need not contain essential elements for binding to the immunophilin proteins, and may be selected from a very broad range of structural types" (emphasis added, see page 2, lines 22-23 of Holt). Although Holt provides a cell-based transfection assay in pages 48-49, there does not appear to be relevant teaching in Holt as to *which* of the numerous types of linkers are preferred for *any* reason.

This pertains to the issue of "obviousness of species when prior art teaches genus." *See* MPEP 2144.08: "[o]ffice personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., Ochiai*, 71 F.3d at 1569-70, 37 USPQ2d at 1131; *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ('[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art.' (emphasis in original)); ... *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ('The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.')"

Also pursuant to MPEP 2144.08, "...a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.' *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)."

Here, there is no teaching in Holt that would suggest that the PEG linkers would increase cellular uptake of the hybrid ligands despite its hydrophilic structure, as Applicants have shown. In other words, the cited art (Holt) would not motivate a skilled artisan to select the subgenus of PEG linkers from the numerous disclosed linker genus. Furthermore, a skilled person also would not have chosen a PEG linker-based construct when seeking to solve the technical problem of providing an improved membrane permeable heterodimeric hybrid ligand useful for *in vivo* application, such as the screening methods of Liu. The skilled artisan would have assumed that such a construct would not be useful due to the high water solubility of the PEG linkers, as evidenced by Bertozzi, and, thus, reduced membrane permeability resulting from using the PEG moiety.

On the other hand, the unexpected results Applicants have shown are sufficient to rebut the argument of obviousness.

Therefore, reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**, under Order No. **DFMP-P01-018**.

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Respectfully submitted,

By _____

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